

**THE BOARD OF PATENT APPEALS AND INTERFERENCE
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of:	Man <i>et al.</i>	Confirmation No.:	7683
Serial No.:	10/685,942	Art Unit:	1614
Filed:	October 14, 2003	Examiner:	Rae, C.
For:	Pharmaceutically Active Isoindoline Derivatives	Attorney Docket No:	9516-205-999
		CAM:	501872-999204

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the provisions of 35 U.S.C. §134 and 37 C.F.R. 41.37, an appeal is taken herein from the final rejection dated July 9, 2008, which rejects claims 1, 5, and 7-8 of this application. A Notice of Appeal was filed in connection with this application on October 8, 2008 with provision for the appropriate fee, and thus, this Brief on Appeal is timely filed.

Also submitted herewith is the fee under 37 C.F.R. §41.20(b)(2), which will be paid electronically via EFS Web.

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I. REAL PARTY IN INTEREST

The real party in interest is Celgene Corporation, the assignee of record of the above-identified application.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their legal representatives respectfully submit that they are not aware of any appeals, interferences, or judicial proceedings that may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1, 5, and 7-8 of this application are under final rejection.

Claims 2-4 and 6 were previously canceled without prejudice in connection with a restriction requirement dated July 7, 2004.

New claims 7-8 were added in Appellants' amendment dated October 31, 2007.

Claims 1, 5, and 7-8 are the subject of this appeal.

IV. STATUS OF AMENDMENTS

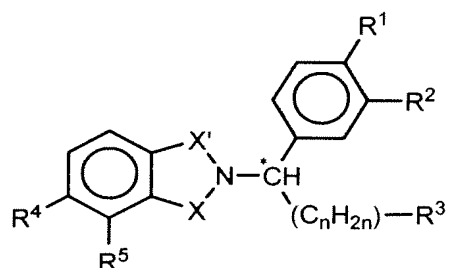
No claim amendments are made in this paper, and thus, no new matter is added.

A listing of claims, showing the claims on appeal, are presented in the **CLAIMS APPENDIX** of this paper.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claims pending in this application generally recite methods of reducing elevated levels of PDE IV in a mammal, or methods of treating an inflammatory or an autoimmune disease in a mammal, which comprise administration of certain chemical compounds. The subject matter recited by each of the pending claims is summarized below.

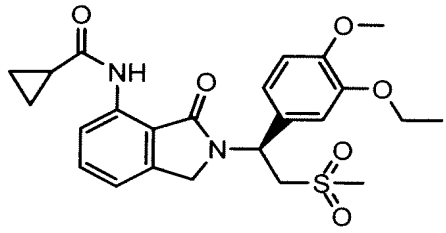
Claim 1 recites a method of reducing elevated levels of PDE IV in a mammal, which comprises administering thereto an effective amount of a compound of the following formula:



or an acid addition salt or a substantially chirally pure isomer thereof, wherein the variables are defined in the claim. This claim is described, for example, on page 1, lines 7-8, page 10 line 11 – page 12, line 12, and page 12, lines 15-17 of the specification.

Claim 5 recites a method of treating an inflammatory or an autoimmune disease in a mammal, which comprises administering thereto an effective amount of a compound recited by claim 1. This claim is described, for example, on page 1, lines 10-11, page 10 line 11 – page 12, line 12, and page 12, lines 15-17 of the specification.

Claim 7 recites a method of reducing elevated levels of PDE IV in a mammal, which comprises administering thereto an effective amount of a compound of the formula:



or an acid addition salt thereof. The compound recited by claim 7 is within the scope of the genus recited by claim 1. This claim is described, for example, on page 1, lines 7-8 and page 69, Example 57 of the specification.

Claim 8 recites a method of treating an inflammatory or an autoimmune disease in a mammal, which comprises administering thereto an effective amount of a compound recited by claim 7. This claim is described, for example, on page 1, lines 10-11 and page 69, Example 57 of the specification.

VI. GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are whether the Examiner's rejection of claims 1, 5, and 7-8 as allegedly not enabled is legally improper in view of *In re Brana*, which is uniquely

related to this case and whether the Examiner erred in rejection the claims under the judicially-created doctrine of obviousness-type double patenting over claims 47-70 of U.S. Patent Application No. 10/786,822, particularly in view of the controlling case law, *e.g.*, *Takeda* and *Eisai*.

Specific issues for consideration in this appeal to this Board are:

A. Whether the Examiner erred in rejecting claims 1 and 7 as allegedly not enabled despite the fact that the claims recite methods of reducing an elevated level of PDE IV, and test data showing the efficacy of several representative compounds in reducing the level of PDE IV were indeed provided during the prosecution;

- Whether the rejection of claim 1 is improper where the claim recites a genus of compounds and PDE IV data for several representative compounds encompassed by that genus were provided;
- Whether the rejection of claim 7 is improper where the claim recites a single compound and the data for that single compound was provided;

B. Whether the Examiner erred in rejecting claims 5 and 8 as allegedly not enabled despite the fact that the involvement of PDE IV in inflammatory or autoimmune diseases was known in the art and provided in the specification, and test data showing the efficacy of several representative compounds in reducing PDE IV were submitted during the prosecution;

- Whether the rejection of claim 5 is improper where the claim recites a genus of compounds and PDE IV data for several representative compounds encompassed by that genus were provided;
- Whether the rejection of claim 8 is improper where the claim recites a single compound and the data for that single compound was provided; and

C. Whether the Examiner erred in rejecting claims 1, 5, and 7-8 under the obviousness-type double patenting over claims 47-70 of U.S. Application No. 10/786,822 (“the ‘822 application”)¹. In particular, whether the allegation made in connection with this rejection that the claims of the ‘822 application render the current claims “obvious” merely

¹ Appellants respectfully point out that the ‘822 application issued as U.S. Patent No. 7,345,062, without claims 47-70. However, a continuation application containing claims 47-70 has been filed from the ‘822 application, and was accorded a serial number 12/009,182.

based on alleged “structural similarity,” despite the fact that the structures recited by the claims of the ‘822 application and the pending claims have completely difference structures with regard to position R³, can be sustained. In addition, whether the inhibition of PDE IV, TNF α , MMP, or undesired angiogenesis, as recited by claims 47-70 of the ‘822 application, would be patentably indistinct from the treatment of an inflammatory or an autoimmune disease, as recited by the pending claims 5 and 8.

VII. ARGUMENT

A. Background of the Invention

Many cellular functions are reported to be mediated by levels of adenosine 3',5'-cyclic monophosphate (cAMP). The primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases (PDE). (Specification, page 9, citing Beavo *et al.*, *Trends in Pharm.*, 11: 150-155 (1990)). Among the family members of PDE, PDE IV is known to be particularly effective in, among others, inhibition of the inflammatory mediator release. (*Id.*). Thus, reducing PDE IV would “constitute valuable therapeutic strategies for the treatment of many diseases and disorders, including inflammatory and autoimmune diseases. (*Id.*, pages 9-10). The compounds recited by the claims pending in this application are “useful in the inhibition of phosphodiesterases, particularly ... PDE IV,” and thus, useful “in the treatment of disease states mediated thereby.” (*Id.*, page 9).

B. Summary of Prosecution History.

This application was filed on October 14, 2003 as continuation of U.S. Application No. 09/708,199, now U.S. Patent No. 6,667,316 (“the ‘316 patent), and was accorded a serial number 10/685,942. As originally filed, this application contained 6 claims, directed generally to methods of reducing elevated levels of PDE IV (claim 1), TNF α (claim 2), and matrix metalloproteinase (claim 3) and methods of treating disorders associated with PDE IV (claim 5), TNF α (claim 4), and matrix metalloproteinase (claim 6).

In a restriction requirement issued on July 7, 2004, the claims were restricted to one of three groups: Group I directed to methods of reducing PDE IV and treating disorders associated therewith; Group II directed to methods of reducing TNF α and treating disorders

associated therewith; and Group III directed to methods of reducing matrix metalloproteinase and treating disorders associated therewith. In Appellants' response of September 7, 2004, claims in Group I were provisionally selected, and cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindoline-4-yl}caboxamide, the compound (*albeit* with no stereochemical designation) recited by the pending claims 7-8, was elected in connection with the species election requirement.

An Office Action issued on January 10, 2005 by Examiner K. Weddington who no longer is the examiner in the current application. In the office action, claims 1 and 5 were rejected under the non-statutory obviousness-type double patenting over the '316 patent. Despite the fact that the claims of the '316 patent recite compounds and compositions, it was alleged that the methods of use recited by claims 1 and 5 were patentably indistinct from the compounds because the '316 specification "teaches [in] its specification ... that the instant compounds inhibit PDE IV, [and] treat inflammatory diseases and/or autoimmune diseases. (January 10 OA, page 3). Additionally, claims 1 and 5 were rejected as allegedly not enabled based on the Examiner's analysis of the factors set forth in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) ("the *Wands* factors"). The analysis provided, among others, that the "reducing elevated levels of PDE IV" and "treating an inflammatory or autoimmune disease" are "highly unpredictable and unreliable" (*Id.*, page 4), and that no working examples are provided in the specification. (*Id.*, page 5).

Appellants filed a Response on April 18, 2005. With regard to the rejection under the obviousness-type double patenting, it was pointed out that the rejection is improper because the claims in the '316 patent, which recite composition of matter, are patentably distinct from claims 1 and 5 of the present application, which recite methods of use. (April 18 Response, page 7). Further, it was also pointed out that the Examiner's reliance on the specification of the '316 patent was legally improper. (*Id.*). With regard to the enablement rejection, it was pointed out that: 1) the specification provides sufficient information for those skilled in the art to practice the claimed methods; 2) no objective evidence was provided in the office action that would render the presumption of enablement doubtful; and 3) no undue experimentation is necessary for the practice of the claimed methods. (*Id.*, pages 8-10).

A Final Office Action issued on June 29, 2005, in which Appellants' submission regarding obviousness-type double patenting was dismissed based on the allegation that "the

method claims of the present application” is “an obvious variation of the [compounds claimed in the ‘316 patent] since the method claims cannot function without the compounds of” the ‘316 patent. (June 29 OA, pages 2-3). In addition, the rejection based on the enablement requirement was maintained based on the allegation that “[a]bsent reasonable a priori expectation of success, one skilled in the art would have to test extensively many conditions that may cause elevated PDE levels, many conditions that may cause an inflammatory disease, and ... many conditions that may cause an autoimmune disease.” (*Id.*, page 5).

Appellants, in their Response dated September 27, 2005, again pointed out that the rejection under the obviousness-type double patenting was legally improper because neither the specification of the ‘316 patent nor Appellants’ own disclosure in the current application may be used to form a basis of the rejection. (September 27 Response, page 2). Further, in connection with the enablement rejection, Appellants pointed out that compliance with the enablement rejection does not turn on whether an example is disclosed. (*Id.*, page 3). Moreover, Appellants provided test results summarizing IC₅₀ values for PDE IV in connection with certain exemplary compounds encompassed by the genus recited by claims 1 and 5, and pointed out that, to the extent that there was any doubt with regard to the enablement of the claimed methods, the test results showed that the claimed methods were indeed enabled. (*Id.*, pages 4-5).

In an Advisory Action issued on November 2, 2005, the rejection under the obviousness-type double patenting was withdrawn, but the rejection based on the enablement requirement was maintained.

Appellants filed a Request for Continued Examination and another Response on January 19, 2006. In their Response, Appellants reiterated the fact that the specification provides sufficient guidance to those skilled in the art to practice the claimed methods and resubmitted the PDE IV inhibition data, which was originally submitted in their previous response. (January 19 Response, pages 2-4). In addition, based on the legal principles set forth in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), Appellants pointed out that the fact that further research and development are required cannot be the basis for rejecting a claim as not enabled because the *Brana* court recognized the necessity of further research and development particularly in connection with pharmaceutical inventions and held that FDA approval cannot be a prerequisite for patentability. (*Id.*, pages 4-5).

In a subsequent Office Action issued on April 24, 2006, the Examiner reinstated the rejection under the obviousness-type double patenting providing reasons substantially identical to those set forth in previous office actions. (April 24 OA, pages 2-3). Further, also providing reasons substantially identical to those provided in previous office actions, the rejection based on the enablement requirement was also maintained. (*Id.*, pages 3-5). Notably, no reference or comment was made in connection with the test data submitted in Appellants' responses.

In a Response dated June 28, 2006, Appellants again pointed out that the obviousness-type double patenting was legally improper due to the Examiner's improper reliance on the specification of the '316 patent in rejecting the claims. (June 28 Response, pages 2-3). In connection with the enablement rejection, Appellants: 1) resubmitted the test results of certain exemplary compounds and requested that the results be considered; 2) provided a more detailed discussion of the *Brana* case and illustrated that the rejection was improper in view of the legal principles set forth therein; and 3) the specification provides sufficient guidance to those skilled in the art. (*Id.*, pages 4-11).

Another Office Action issued on January 24, 2007 by Examiner C. Rae who is currently the Examiner of this application. With regard to the rejection under the obviousness-type double patenting, it was alleged that the reliance on the '316 specification is proper because "the specification is being used only as a 'dictionary' to determine the meaning of the claim limitations." (January 24 OA, pages 3-4) (emphasis in original). In particular, it is alleged that the specification was referred to to interpret the meaning of "undesirable angiogenesis," as recited by claim 14 of the '316 patent, and it was concluded that the term "undesired angiogenesis," when considered in connection with the '316 patent, would somehow encompass the reduction of PDE IV and the treatment of an inflammatory or an autoimmune disease, as recited by claims 1 and 5 of the present application. (*Id.*, pages 4-5).

With regard to the enablement rejection, it was alleged that there was "doubts ... regarding extrapolation of an [in] vitro method for evaluating the PDE IV inhibitory effects ... to an in vivo method of treating an inflammatory disease or an autoimmune disease." (*Id.*, page 6). In particular, citing Bielekova *et al.*, *The Journal of Immunology*, 164: 1117-1124 (2000) ("Bielekova") and relying on the portion of Bielekova wherein it is purportedly

disclosed that “the simple extrapolation of therapeutic efficacy from animal models to human disorders is not easily feasible,” the Examiner alleged that there was “reason to doubt” the enablement of claims 1 and 5. (*Id.*, pages 8-10).

In their Response dated April 24, 2007, Appellants pointed out that the obviousness-type double patenting is still improper because the term “undesired angiogenesis,” even when read in connection with the ‘316 specification, does not encompass the reduction of PDE IV or the treatment of an inflammatory or an autoimmune disease because each of these limitations are clearly disclosed as separate embodiments in the ‘316 specification. (April 24 Response, page 2). Further, it was pointed out that the portions of the ‘316 specification relied on by the Examiner, even assuming such reliance is legally proper, do not render the reduction of PDE IV or the treatment of an inflammatory or an autoimmune disease obvious so as to make them patentably indistinct from the method recited by claim 14 of the ‘316 patent. (*Id.*, page 3).

With regard to the enablement rejection, Appellants pointed out that the presumption of enablement was not rebutted by the office action because no proper “reason to doubt” was provided in the office action. (*Id.*, pages 4-5). In particular, it was pointed out that the *Brana* case considered facts similar to those presented in this application and held that the enablement requirement is satisfied even if a reference discloses that the test provided in a patent application may not be indicative of the therapeutic value in humans. (*Id.*). Specifically, Appellants pointed out that the *Brana* court clearly stated that the test compounds’ “ultimate value in humans” cannot be required in assessing patentability. (*Id.*).

An Advisory Action issued on May 18, 2007, simply dismissing Appellants’ previous submission as unpersuasive.

Appellants filed a second Request for Continued Examination and a Response on July 20, 2007. The substance of the July 20 response was substantially similar to that of Appellants’ response dated April 24, 2007.

Another Final Office Action issued on September 10, 2007, in which the same reasoning with regard to the obviousness-type double patenting and the enablement requirement. Notably, with regard to the obviousness-type double patenting, the Examiner dismissed Appellants’ previous submission simply by asserting, without really addressing the

substance of Appellants' submission, that the use of the '316 specification was proper because the use was "limited only to its use as a 'dictionary'." (September 10 OA, page 3). With regard to the enablement rejection, the Examiner found Appellants' submission unpersuasive, alleging that the facts of the *Brana* case are distinguishable from those presented in this application. (*Id.*, pages 5-6).

Thereafter, the issues were discussed in an in-person interview held on October 9, 2007. As summarized in "Applicants' Statement of the Substance of the Interview," which was provided in Appellants' Response dated October 31, 2007², it was agreed during the meeting that, to the extent that the PDE IV inhibition properties of certain exemplary compounds had been provided during the prosecution, claim 1, which recites, in part, the reduction of PDE IV, would be allowable. Further, with regard to claim 5, which recites the treatment of an inflammatory or an autoimmune disease, it was agreed that Appellants would provide certain references that show that the modulation of PDE IV is implicated with the treatment of various inflammatory or autoimmune diseases. Such references were indeed provided in Appellants' response of October 9. (October 9 Response, page 8). In connection with the rejection under the obviousness-type double patenting, a terminal disclaimer over the '316 patent was filed to expedite the prosecution. (*Id.*, page 7). Lastly, claims 7 and 8, both of which recite, in part, a specific compound encompassed by the genus recited by claims 1 and 5, were added in Appellants' response.

In a Non-final Action issued on December 28, 2007, the rejection under the obviousness-type double patenting was withdrawn in response to the previously filed terminal disclaimer. The rejection based on the enablement requirement, however, was maintained. The reasons provided were: 1) compounds and diseases recited by the claims are very broad; 2) "the term 'method for reducing elevated levels of PDE IV in mammal' ... does not require the presence [of] any pathologic condition"; and 3) the legal principles set forth in *Brana* are inapplicable to this application. (December 28 OA, pages 4-6).

Notably, a new rejection under the non-statutory doctrine of obviousness-type double patent was raised in the office action. Specifically, the claims were rejected as allegedly patentably indistinct from claims 47-70 of the '822 application.

² The response was filed along with a third Request for Continued Examination.

In a Response filed on March 25, 2008, Appellants first pointed out in connection with the enablement rejection that, at the very least, claims 1 and 7 should be patentable regardless of the reasoning provided by the Examiner in the previous office action because claims 1 and 7 recite a specific compound. (March 25 Response, page 2). Further, in connection with the rejection of claims 5 and 8, Appellants reiterated that: 1) the legal principles set forth in *Brana* are indeed applicable to this application; and 2) no proper reason to doubt was provided by the Examiner. (*Id.*, pages 3-6). In connection with the rejection under the obviousness-type double patenting, Appellants pointed out that the claims pending in this application are clearly patentably distinct from those in the '822 application, at least because the claims of the '822 application recite compounds that have a substantially different structure with regard to R³ position of the currently recited compounds. (*Id.*, page 7).

Despite the response, a Final Office Action issued on July 9, 2008 ("the Office Action"), essentially reiterating the same reasoning provided in previous office actions. This appeal followed.

C. The Examiner Erred in Rejecting Claims 1, 5, and 7-8 Under 35 U.S.C. § 112, ¶1

Appellants respectfully submit that the Examiner erred in rejecting the subject matter recited in instant claims 1, 5, and 7-8 as allegedly not enabled. As the prosecution currently stands, the rejection is premised on the allegation that undue experimentation is required based on the following analysis of the *Wands* factors:

- 1) Bielekova allegedly provides "reason to doubt" the enablement by illustrating "unpredictability or uncertainty in the art" (Office Action, pages 8-10);
- 2) since the working examples provided are "limited to in vitro experiments," "specific direction or guidance only for an in vitro methodology for evaluating PDE IV inhibitory effects" was provided (*Id.*, page 11) ;
- 3) claims 1 and 5 are allegedly very broad as to encompass "multiple variants of the elected compound" and "various diverse conditions involving unregulated angiogenesis" (*Id.*);

- 4) although claims 7 and 8 recite a single compound, “how the chemical feature of said compound relates to the multiplicity of immunopathologies encompassed by these claims are unclear” (*Id.*); and
- 5) the claimed methods of treatment “may differ in terms of method of administration, dose level, [and] dosage regimen,” and thus, “coupled with the complex and different immunopathologies associated with inflammatory and autoimmune diseases, ... it is reasonable to surmise that this level of uncertainty and unpredictability in the art would require” more than routine experimentation. (*Id.*, page 12).

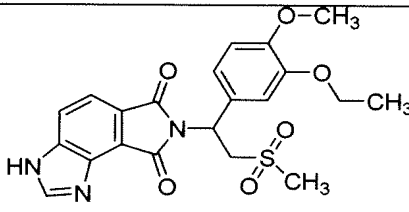
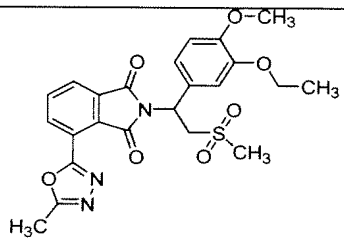
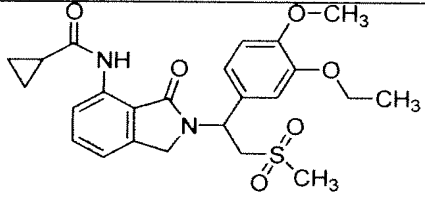
Appellants respectfully disagree with each of these allegations, and submit that no undue experimentation is required to practice the claimed methods for the following reasons.

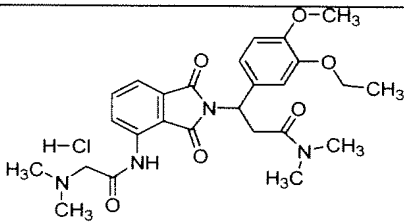
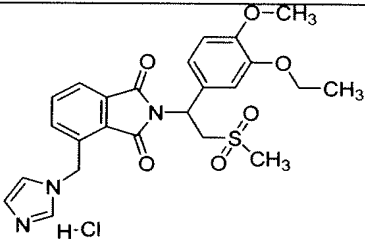
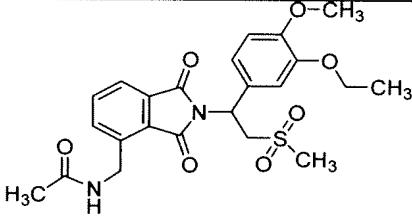
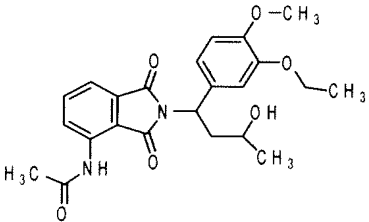
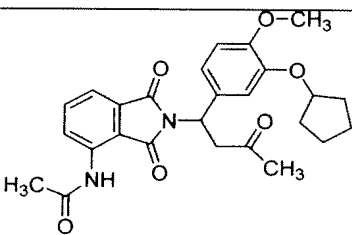
As well settled, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. (*U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. (*In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Furthermore, “[a] specification disclosure...must be taken as being in compliance with the enablement requirement...unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” (Manual of Patent Examining Procedure (“MPEP”) § 2164.04) (emphasis added). Moreover, “not everything necessary to practice the invention need be disclosed. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.” (*Id.*, § 2164.08) (emphasis added).

At the outset, Appellants respectfully submit that the claims pending in this application are clearly enabled because the specification “contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented.” (*Id.*, § 2164.04). For example, the specification teaches that PDE IV can be inhibited using compounds of the invention. (Specification, page 24, lines 10-11). Likewise, the specification teaches that an inflammatory or autoimmune disease can be treated by using compounds of the invention.

(*Id.*, lines 14-15). Methods of preparing the compounds are described in detail on pages 13-17 of the specification, as well as in the Examples section of this application. Dosages and routes of administration are described, for example, on pages 23-24 of the specification. All that is required for those of ordinary skill in the art to practice the claimed invention is to administer the specified amount of the specified compound using the specified routes of administration. Therefore, it is clear that the application provides sufficient guidance to allow those of ordinary skill in the art to make and use the claimed invention.

Furthermore, for avoidance of any doubt, Appellants provided in their responses *in vitro* data showing the efficacy of certain exemplary compounds in reducing the PDE IV. (See, e.g., Appellants' responses dated January 19, 2006 and September 27, 2005). The data provided during the prosecution are reproduced below:

Example #	Structure	PDE 4 IC ₅₀ (μM)
3		0.356
15		0.658
55		0.278

61		0.287
65		0.095
66		0.105
71		0.543
76		0.198

The data shown above are further evidence that the compounds recited by the pending claims are indeed effective in inhibiting PDE IV, and thus, the claimed methods are indeed enabled.

1. No proper “reason to doubt” the enablement is provided

Despite the above, the Examiner alleges that the presumption of enablement is rebutted in this application based on the assertion that “there is reason to doubt the objective

truth of the statements contained” in this application. (*Id.*) Bielekova, which is attached hereto as **Exhibit A**, was provided to support this allegation. (*Id.*, page 9-10). In addition, along the same line, the Examiner alleges that the data shown above, due to the fact that they were obtained *in vitro*, provides “specific direction or guidance only for an in vitro methodology for evaluating PDE IV inhibitory effects.” (*Id.*, page 11) (emphasis added).

However, while passages from Bielekova are extensively reproduced in the Office Action, no explanation as to why the reproduced passages are relevant in determining whether there was a reason to doubt that the claims are enabled. Instead, the only suggestion that Appellants can glimpse from the Office Action is the statement from Bielekova that “simple extrapolation of therapeutic efficacy from animal models to human disorders is not easily feasible.” (Office Action, page 10). Presumably, Appellants believe that it is the Examiner’s position that there was reason to doubt the enablement because Bielekova states that therapeutic efficacy obtained from animal (or any other models, including the *in vitro* tests provided in this application) cannot easily be extrapolated to human disorders.

Regardless of the truth of that particular statement, Appellants respectfully point out that it is legally erroneous to rely on such a statement in rejecting the claims for allegedly failing to satisfy the enablement requirement. This is because the court in *Brana*, a copy of which is attached hereto as **Exhibit B**, considered a substantially identical disclosure made in a prior art reference (*i.e.*, disclosure in a prior art reference that some laboratory oncologists are skeptical about the predictive value of murine tumor models provided by the applicants for human therapy), and concluded that the claims were enabled because the “usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development.” (*Brana*, 51 F.3d at 1568). In reaching this conclusion, the court held that the references that “merely discuss the therapeutic predictive value of [the tests provided by the applicants]” are relevant in assessing the enablement requirement “only if applicants must prove the ultimate value in humans of their asserted utility,” but held that no such requirement exists for the patentability. (*Id.* at 1566) (emphasis added).

Applying the holdings of *Brana* to the current application, Bielekova, especially the portion of Bielekova relied on by the Examiner, precisely discloses what the prior art references at issue in *Brana* disclosed (*i.e.*, that the predictive value of certain non-human

tests in human therapy may be questionable). However, as the *Brana* court plainly puts it, such a disclosure is relevant “only if applicants must prove the ultimate value in humans of their asserted utility,” indicating no requirement to prove the ultimate value in humans exists in connection with patentability. (*Id.*). This is because, according to the *Brana* court, “[t]he stage at which an invention in [the pharmaceutical] field becomes useful is well before it is ready to be administered to humans.” (*Id.* at 1568).

Furthermore, Appellants respectfully submit that the Examiner’s allegation that “specific direction or guidance only for an *in vitro* methodology for evaluating PDE IV inhibitory effects” was provided also cannot stand in view of the legal principles set forth in *Brana* discussed above. Indeed, adopting the Examiner’s rationale, no claims to method of human treatment can be issued based on *in vitro* data, and such a result would be flatly contrary to *Brana* court’s reasoning that “[t]he stage at which an invention in [the pharmaceutical] field becomes useful is well before it is ready to be administered to humans.” (*Brana*, 51 F.3d at 1568)³.

In this regard, the Examiner maintains that the legal principles set forth in *Brana* are inapplicable to this application based on the assertion that: 1) while the issue in *Brana* was “whether ‘asserted utility’ was a proper test for determining enablement under 112, first paragraph,” no such issue is present in the current application (December 27 OA, page 5); and 2) the facts of *Brana* are distinguishable from those in the current application since *Brana*’s determination of anti-cancer activity was obtained using “a well-recognized mouse model,” whereas “no *in vitro* model is well-recognized in the art for reliably and predictably determining the anti-PDE IV activity ... against a specific disease species or the genus of inflammatory and autoimmune diseases.” (*Id.*). Appellants respectfully submit that the Examiner is misinterpreting the *Brana* case.

With regard to the Examiner’s first allegation that the legal issue presented in *Brana* does not exist in the current application, Applicants respectfully wishes to point to page 1564 of *Brana* decision. There, the court clearly indicated that, although the rejection at issue in *Brana* “appears to be based on the issue of whether the compounds had a practical utility, ... the rejection ... stands on the requirements of § 112, ¶ 1.” (*Brana*, 51 F.3d at 1564)

³ Appellants respectfully point out that there are PDE IV inhibitors approved by the FDA, *e.g.*, Ariflo[®]. Although FDA approval is not required for patentability, the fact that there are approved PDE IV inhibitors evidences the fact that PDE IV is a valid target for drug development.

(emphasis added). Thus, the court stated that “it is to that provision that [the court] address” the issue. (*Id.*). In other words, the issue that the court considered and addressed in *Brana* was whether the specification had an enabling disclosure as to the asserted utility of treatment of cancer, an issue substantially identical to the one in this application, *i.e.*, whether the specification had an enabling disclosure as to the claimed utility of the treatment of inflammatory or autoimmune diseases.

In addition, the Examiner also alleges that facts in the current application are distinguishable from those in *Brana* because, according to the Examiner, unlike *Brana*, no well-recognized model for reliably and predictably determining the efficacy for inflammatory and autoimmune diseases is available in the art. (December 27 OA, page 5). First, Appellants respectfully point out that, contrary to the Examiner’s allegation, the murine tumor model provided in the application at issue in *Brana* was not a “well-recognized model for reliably and predictably determining the efficacy” of the test compounds. In fact, issues in *Brana* arose precisely because the reliability and predictability of that model was challenged by the examiner based on a prior art reference. Thus, Appellants respectfully submit that the allegation made by the Examiner in this regard is factually incorrect, and thus, cannot be a basis to distinguish the facts of *Brana* from those of the current application.

Furthermore, Appellants respectfully point out that, to the extent that the challenged murine tumor model was found acceptable in *Brana*, the PDE IV test provided by Appellants during the prosecution is sufficient to establish the enablement of the claimed methods. In this regard, Appellants submitted in their response of October 31, 2007 the following references, which show that PDE IV is implicated with various inflammatory and/or autoimmune diseases: 1) Burnouf *et al.*, *Curr. Pharm. Des.*, 8(14): 1255-96 (2002), attached hereto as **Exhibit C**, which indicates that the PDE IV activity is associated with a wide variety of diseases related to inflammatory state or autoimmune pathology (*see, e.g.*, Abstract); 2) Dastidar *et al.*, *Curr. Opin. Investig. Drugs*, 8(5): 364-72 (2007), attached hereto as **Exhibit D**, which indicates that PDE IV inhibitors’ therapeutic potential in the treatment of various inflammatory disease such as asthma, COPD, psoriasis, rheumatoid arthritis, and inflammatory bowel diseases, *e.g.*, Crohn’s disease and ulcerative colitis (*see, e.g.*, Abstract); and 3) Sommer *et al.*, *J. Neuroimmunol.*, 79(1): 54-61 (1997), attached hereto as **Exhibit E**, which indicates that PDE IV inhibition is advantageous for the treatment of autoimmune

diseases such as multiple sclerosis (*see, e.g.*, Abstract). Appellants respectfully submit that these references clearly demonstrate the therapeutic potential of PDE IV inhibition in a wide variety of autoimmune or inflammatory diseases, and thus, the predictive value of the test results provided by Appellants is sufficiently established by these references.

Consequently, Appellants respectfully submit that the legal principles set forth in *Brana* are entirely applicable to this application, and thus, the alleged “reason to doubt” provided by the Examiner is legally improper.

2. The whole scope of the pending claims are adequately enabled

It is alleged in the Office Action that “the claims are very broad,” presumably indicating that the whole scope of the pending claims is not enabled. (Office Action, page 11). In this regard, it is alleged that “claim 1 encompasses that all mammalian species, multiple variants of the elected compound, ... various diverse conditions involving unregulated angiogenesis⁴, including a heterogen[e]ous group of inflammatory and autoimmune diseases that are characterized by different immunopathologies and etiologies⁵.” (*Id.*). Appellants respectfully submit that none of these allegations with regard to claim 1 can form the basis to question the full enablement of claim 1.

First, although the scope of claim 1 does encompass all mammalian species and multiple variants of the elected compound, Appellants respectfully submit that all mammalian species and multiple variants are adequately enabled by the specification and evidence submitted by Appellants during the prosecution. For example, Appellants respectfully submit that the enablement for the genus recited by claim 1 is sufficiently provided in view of the PDE IV inhibition test results provided by Appellants for various compounds encompassed by the genus. While the Examiner appears to imply, without providing any evidence or reasoning, that the whole scope of the genus recited by claim 1 is not enabled, no explanation as to why the PDE IV test data provided for various representative compounds are not sufficient to provide enablement for the genus recited by claim 1. In addition, with regard to the implication that the no sufficient enablement for “all mammalian species” was provided,

⁴ It is unclear why the Examiner refers to “unregulated angiogenesis” in connection with this analysis. Appellants respectfully point out that “unregulated angiogenesis” is not recited by claim 1.

⁵ Presumably, in this part of the statement, the Examiner is referring to claim 5, which recites the treatment of an inflammatory or an autoimmune disease.

Appellants respectfully point out that the burden of showing that not all mammalian species were enabled lies on the Examiner. As the Examiner fails to provide any evidence or reasoning to support this implication, Appellants respectfully submit that this burden is not met by the Examiner.

Furthermore, while the Examiner alleges that claim 1 encompasses “various diverse conditions involving unregulated angiogenesis,” Appellants respectfully point out that claim 1 recites reduction of PDE IV. It is unclear to Appellants as to what limitations of claim 1 are referred to by the Examiner as encompassing “various diverse conditions.” In this regard, Appellants respectfully submit that there can be no question regarding the enablement of the subject matter recited by claim 1 because claim 1 simply recites, in part, the reduction of PDE IV, and the reduction of PDE IV by various exemplary compounds encompassed by the genus recited by claim 1 was provided by Appellants. Consequently, Appellants respectfully submit that the whole scope of claim 1 is adequately enabled, and no evidence or reasoning to rebut this presumption is provided by the Examiner.

Claim 5 is also implied by the Examiner to be not fully enabled, allegedly because claim 5 encompasses “a heterogen[e]ous group of inflammatory and autoimmune diseases that are characterized by different immunopathologies and etiologies.” (Office Action, page 11). Again, Appellants respectfully submit that such a breadth cannot be equated with the proposition that claim 5 is not fully enabled, especially in view of the fact that Appellants provided ample evidence to show that PDE IV inhibition is implicated with the treatment of various inflammatory or autoimmune diseases.

With regard to claim 7 and 8, while the Examiner recognizes that these claims recite only a single compound, the Examiner indicates that the claims are still not fully enabled allegedly because “how the chemical feature of [the recited compound] relates to the multiplicity of immunopathologies encompassed by these claims are unclear.” (*Id.*). First, Appellants respectfully point out that the Examiner is asserting a requirement that finds no root in any of the known legal principles regarding patentability. In other words, understanding or showing “how the chemical feature of [the claimed compound] relates to” the immunopathologies of the disease the compound purports to treat is completely irrelevant to the patentability of a claim to the treatment of the disease using the compound. By the Examiner’s logic, no claims to the treatment of a disease should be allowable unless one

completely understands the full mechanism of action of the treatment, which is flatly contrary to the legal principles set forth in the *Brana* case. (See *Brana*, 51 F.3d at 1568).

Consequently, Appellants respectfully submit that the breadth of pending claims, in the absence of any evidence or reasoning to rebut the presumption of the enablement provided by the Examiner, cannot be accorded any weight in assessing whether the whole scope of the claims is enabled.

3. No more than routine experimentation is required to practice the claimed methods

It is alleged in the Office Action that the claimed methods of treatment “may differ in terms of method of administration, dose level, [and] dosage regimen,” and thus, “coupled with the complex and different immunopathologies associated with inflammatory and autoimmune diseases, ... it is reasonable to surmise that this level of uncertainty and unpredictability in the art would require” more than routine experimentation. (Office Action, page 12). Appellants disagree.

As discussed above, the specification provides sufficient information and guidance with regard to how to practice the claimed methods. Although the Examiner alleges that some experimentation may be required in connection with “method of administration, dose level, [and] dosage regimen,” Appellants respectfully point out that the optimization of such factors is no more than what is routinely practiced by those skilled in the art, for which the specification provides sufficient guidance. (See, e.g., specification, pages 23-24). Furthermore, Appellants respectfully submit that, even considering the “complex and different immunopathologies associated with inflammatory and autoimmune diseases,” no more than routine experimentation is required by those skilled in the art for the practice of the claimed methods.

In this regard, Appellants respectfully point out that the legal principles set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) provide helpful insight as to whether undue experimentation would be required to optimize the factors referred to by the Examiner. In *Wands*, the Court of Appeals for the Federal Circuit held that claims directed to immunoassay methods were enabled, even though in order to practice the claimed invention one would have to screen “hybridomas to determine which ones secrete antibody with desired

characteristics.” (*Wands*, 858 F.2d at 740). This was because “[p]ractitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.” (*Id.*).

As in *Wands*, the Examiner here is objecting to what is basically a screening step. Yet here, the screening is not nearly as complex as that in *Wands*, as the claimed invention is directed to the use of specific, readily obtainable compounds, for which routes of administration and dosages are set forth in the specification. Moreover, the determination by a physician as to whether a compound is effective in treating a disease in a given patient is a routine determination that is always made by physicians for every pharmaceutical.

Consequently, Appellants respectfully submit that no more than routine experimentation is necessary for the practice of the claimed methods, particularly in view of the direction and guidance provided in the specification and the skill in the art.

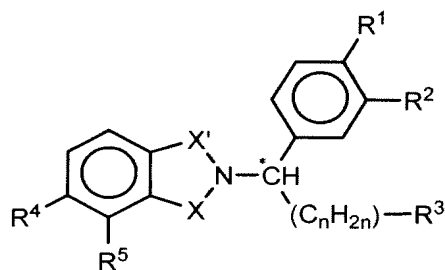
4. Summary

In sum, for the reasons discussed above, the Examiner’s rejection is legally improper under *In re Brana*. Further, the analysis of the *Wands* factors set forth by the Examiner, individually or collectively, is simply not sufficient to rebut the presumption of the enablement. Thus, Appellants respectfully request that the Board overturn the Examiner’s rejection of the claims under 35 U.S.C. § 112, ¶1.

D. The Examiner Erred in Rejecting the Claims Under the Non-Statutory Doctrine of Obviousness-Type Double Patenting

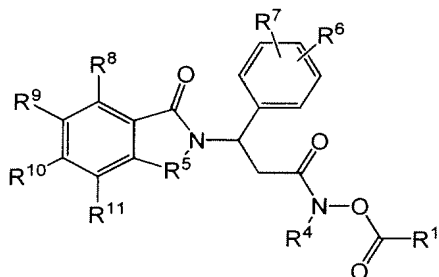
Claims 1, 5, and 7-8 are rejected under the obviousness-type double patenting over claims 47-70 of the ‘822 application. In particular, it is alleged that the pending claims are not patentably distinct from the claims of the ‘822 application allegedly because “the instant claims ... are deemed to be obvious variants of the referenced claims.” (Office Action, page 13).

Claims 1 and 5 of the current application recite, in part, a compound of the following formula:



wherein, among others, R^3 is $-SO_2-Y$, $-COZ$, $-CN$, or hydroalkyl of 1 to 6 carbon atoms in which Z is $NR^{6''}R^{7''}$, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl; $R^{6''}$ is hydrogen, alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, phenyl, benzyl, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, or alkylamino of 1 to 4 carbon atoms; and $R^{7''}$ is alkyl of 1 to 4 carbon atoms.

In contrast, the compound recited by claims 47-70 of the '822 application has the formula:



As can be seen by comparing the two structures, the genus structures recited by claims 47-70 of the '822 application do not even overlap with the genus structure recited by the pending claims. In particular, it is pointed out that the R^3 position of the currently recited genus cannot be $-CO-(NR^4)-O-CO-R^1$ as required by the genus structures recited by claims 47-70 of the '822 application. Therefore, in view of these structural differences, Appellants respectfully submit that the pending claims should be patentably distinct from claims 47-70 of the '822 application.

Despite this, while acknowledging that "the genus structures of the instant claims and the reference claims differ with respect to R3," the Examiner asserts that the pending claims are patentably indistinct from the claims of the '822 application based on the assertion that "it would have been obvious to one of ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those of the instant

claims, because an ordinary artisan would have reasonable expectation that any of the species of the genus would have similar properties.” (Office Action, pages 4-5) (emphasis added).

In this regard, Appellants respectfully point out that the Examiner appears to have misunderstood the chemical structures recited by the pending claims and the claims of the ‘822 application. To clarify, it is respectfully pointed out that any species that may be selected from the genus recited by the claims of the ‘822 patent cannot “include those of the instant claims” because the two structures differ on the R³ position so that there can be no overlap between the structures. Consequently, to the extent that the allegation that the current claims are patentably indistinct from those of the ‘822 application is based on the Examiner’s misunderstanding of the structures recited by the claims, Appellants respectfully submit that the rejection of the claims under the obviousness-type double patenting should be overturned.

In addition, to the extent that the Examiner’s rejection may be relying on the allegation of “structural similarity,” Appellants respectfully point out that the rejection also cannot stand in view of the controlling legal principles regarding the obviousness of “structurally similar” compounds. (*See, e.g., Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 1739 (2008)). Specifically, allegations of “structural similarity” are not enough to render a structural modification obvious because, as the Federal Circuit emphasized, “it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.” (*Id.* at 1357 (emphasis added); *see also Eisai Co., Ltd. v. Dr. Reddy’s Laboratories, Ltd.*, No. 2007-1397 (Fed. Cir. Jul. 21, 2008) (“the record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution.”)).

Thus, while the controlling legal principles require that a *prima facie* case of obviousness be supported by “structural similarity” together with a reason to modify, all that is provided in the Office Action is a mere conclusory allegation that the compounds recited by the pending claims are “deemed to be obvious variants of the referenced claims.” (Office Action, page 13). As such, no *prima facie* showing that the subject matter claimed by the pending claims is obvious over, and thus, patentably indistinct from, the subject matter recited by the claims of the ‘822 application is established by the Office Action. For this

additional reason, Appellants respectfully request the Board to overturn the rejection under the obviousness-type double patenting.

E. Conclusion

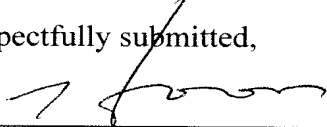
For the reasons discussed above, Appellants respectfully submit that the Examiner erred in rejecting the subject matter of the instant claims. Appellants, therefore, respectfully request that the Examiner's rejections be overturned and that the pending claims be allowed.

No fee is believed due for the submission of this paper. If any fees are required, the Director is authorized to charge such fees to Deposit Account No. 50-3013.

Date: February 4, 2009

Respectfully submitted,

By: Haan Choi
(Lid. Reg. No. 60209)



Anthony M. Insogna

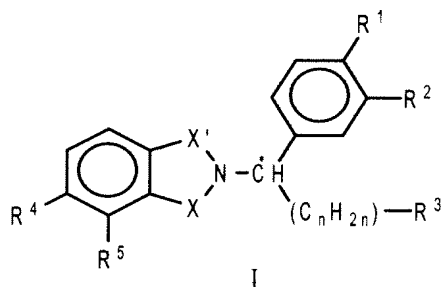
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VIII. CLAIMS APPENDIX

1. (Previously presented) A method of reducing elevated levels of PDE IV in a mammal, which comprises administering thereto an effective amount of a compound of formula (I):



or an acid addition salt or a substantially chirally pure isomer thereof,
wherein:

each of R^1 and R^2 , independently of the other, is alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, cycloalkoxy of 3 to 18 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, or cycloalkylmethoxy in which cycloalkyl has from 3 to 18 carbon atoms;

one of X and X' is $=C=O$ and the other of X and X' is $=C=O$ or $=CH_2$;

R^3 is $-SO_2-Y$, $-COZ$, $-CN$, or hydroalkyl of 1 to 6 carbon atoms in which

Y is alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

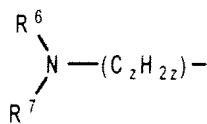
Z is $-NR^{6''}R^{7''}$, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

$R^{6''}$ is hydrogen, alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, phenyl, benzyl, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, or alkylamino of 1 to 4 carbon atoms;

$R^{7''}$ is alkyl of 1 to 4 carbon atoms;

n is 1, 2, or 3;

one of R^4 and R^5 is hydrogen and the other of R^4 and R^5 is imidazolyl, pyrrolyl, oxadiazolyl, triazolyl, or



in which z is 0 or 1;

R^6 , when taken independently of R^7 , is selected from cycloalkanoyl of 2 to 6 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; and

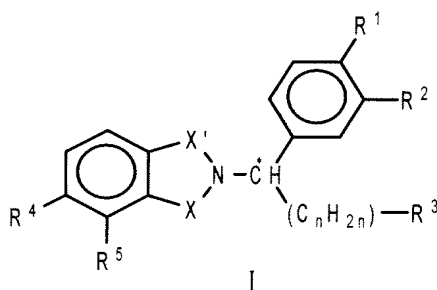
R^7 is hydrogen, alkyl of 1 to 4 carbon atoms, methylsulfonyl, or alkoxyalkylcarbonyl of 2 to 5 carbon atoms; or

R^6 and R^7 , taken together, are alkylidene of 1 or 2 carbon atoms substituted by amino, alkylamino, or dialkylamino, in which each alkyl group has from 1 to 4 carbon atoms, or, provided z is 1, $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, or $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$; and,

the carbon atom designated * constitutes a center of chirality.

2-4. (Canceled).

5. (Previously presented) A method of treating an inflammatory disease or an autoimmune disease in a mammal, which comprises administering thereto an effective amount of a compound of formula (I):



or an acid addition salt or a substantially chirally pure isomer thereof,
wherein:

each of R^1 and R^2 , independently of the other, is alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, cycloalkoxy of 3 to 18 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, or cycloalkylmethoxy in which cycloalkyl has from 3 to 18 carbon atoms;

one of X and X' is $=\text{C}=\text{O}$ and the other of X and X' is $=\text{C}=\text{O}$ or $=\text{CH}_2$;

R^3 is $-\text{SO}_2-\text{Y}$, $-\text{COZ}$, $-\text{CN}$, or hydroalkyl of 1 to 6 carbon atoms in which Y is alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

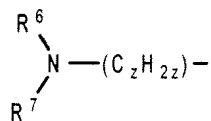
Z is $-NR^{6''}R^{7''}$, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

$R^{6''}$ is hydrogen, alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, phenyl, benzyl, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, or alkylamino of 1 to 4 carbon atoms;

$R^{7''}$ is alkyl of 1 to 4 carbon atoms;

n is 1, 2, or 3;

one of R^4 and R^5 is hydrogen and the other of R^4 and R^5 is imidazolyl, pyrrolyl, oxadiazolyl, triazolyl, or



in which z is 0 or 1;

R^6 , when taken independently of R^7 , is selected from cycloalkanoyl of 2 to 6 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; and

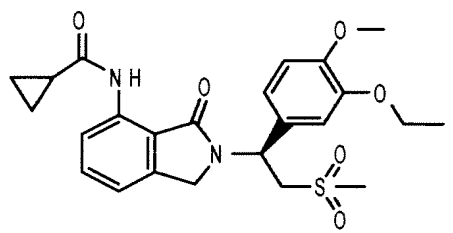
R^7 is hydrogen, alkyl of 1 to 4 carbon atoms, methylsulfonyl, or alkoxyalkylcarbonyl of 2 to 5 carbon atoms; or

R^6 and R^7 , taken together, are alkylidene of 1 or 2 carbon atoms substituted by amino, alkylamino, or dialkylamino, in which each alkyl group has from 1 to 4 carbon atoms, or, provided z is 1, $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, or $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$; and,

the carbon atom designated * constitutes a center of chirality.

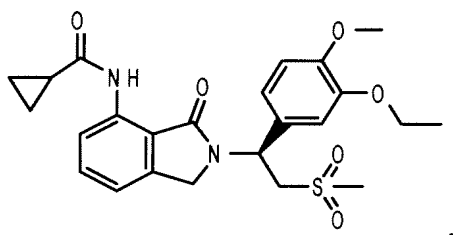
6. (Canceled).

7. (Previously presented) A method of reducing elevated levels of PDE IV in a mammal, which comprises administering thereto an effective amount of a compound of formula:



or an acid addition salt thereof.

8. (Previously presented) A method of treating an inflammatory disease or an autoimmune disease in a mammal, which comprises administering thereto an effective amount of a compound of formula:



or an acid addition salt thereof.

IX. EVIDENCE APPENDIX

Exhibit A: Bielekova *et al.*, *The Journal of Immunology*, 164: 1117-1124 (2000)

Exhibit B: *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995)

Exhibit C: Burnouf *et al.*, *Curr. Pharm. Des.*, 8(14): 1255-1296 (2002)

Exhibit D: Dastidar *et al.*, *Curr. Opin. Investig. Drugs*, 8(5): 364-372 (2007)

Exhibit E: Sommer *et al.*, *J. Neuroimmunol.*, 79(1): 54-61 (1997)

X. RELATED PROCEEDINGS APPENDIX

None.